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IN THE UNITED STATES PATENT AND TRADEMARK OFFICE
BEFORE THE BOARD OF PATENT APPEALS AND INTERFERENCES

IN RE: ROTHSCHILD et al.	
	APPEAL NO. _____
SERIAL NO: 09/900,063	
FOR: PROLACTIN RECEPTOR GENE AS A GENETIC MARKER FOR INCREASED LITTER SIZE IN ANIMALS	**BRIEF ON APPEAL**
FILED: July 6, 2001	
GROUP ART UNIT: 1634	

To the Commissioner of Patents and Trademarks
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Dear Sirs:

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I. INTRODUCTION

This is an appeal of the Final Rejection dated July 23, 2003, finally rejecting claims 1-3, 7-11, 14, 16-20, 26-29, 36-38, 40, 41, 45, 49, 54, and 55. Applicants filed an Amendment after Final dated October 23, 2003 which canceled claims 7, 14, 18, 40, 41, 45, and 49. This Amendment after Final was entered by the Examiner in the Advisory Action dated November 7, 2003. The appealed claims 1-3, 8-11, 16, 17, 19, 20, 26-29, 36-38, 54, and 55 are set forth in an attached Appendix.

II. REAL PARTY OF INTEREST

The real party of interest in the present appeal is Iowa State University Research Foundation, Inc.

III. RELATED APPEALS AND INTERFERENCES

There are no related appeals or interferences.

IV. STATUS OF CLAIMS

Claims 1-40 were originally submitted July 6, 2001. In an amendment dated June 2, 2003, Appellant amended claims 1, 3, 11, 20, 24, 26, 36, 37, and 40, canceled claims 30-34, and added claims 41-55. In a second amendment dated October 23, 2003, Appellant amended claims 1, 16, 17, 19, 20, 26, 27, 29, 37, and 54, and canceled claims 7, 14, 18, 40, 41, 45, and 49. Claims 4-6, 12, 13, 15, 21-25, 35, 39 were withdrawn from consideration by the Examiner in the Office Action dated January 6, 2003 as being drawn to nonelected groups or species. Claims 42-44, 46-48, and 50-53 were withdrawn from

consideration by the Examiner in the Office Action dated July 23, 2003 as being drawn to nonelected groups or species.

The claims here appealed are claims 1-3, 8-11, 16, 17, 19, 20, 26-29, 36-38, 54, and 55.

V. STATUS OF AMENDMENTS

An Amendment After Final Rejection was filed by mail on October 23, 2003. This Amendment After Final Rejection was entered by the Examiner in an Advisory Action dated November 7, 2003. According to the Examiner, the reply failed to place the application in condition for allowance. A Notice of Appeal was timely filed on November 24, 2003.

VI. SUMMARY OF INVENTION

The present invention relates to the discovery that the prolactin receptor (PRLR) gene is a major effect gene for litter size, i.e. that the variation in the PRLR gene can have a quantitative phenotypic effect on the litter size. (specification, p. 4). Animals which are more likely to produce larger litters may thus be identified by assaying for variability within this gene and correlating this variability to the litter size. (specification, p. 5).

Prolactin itself is an anterior pituitary peptide hormone involved in many aspects of an animal's reproductive success. Prolactin activity is mediated by its receptor (PRLR), a member of the cytokine/GHR/PRLR superfamily. (specification, p. 3). Upon the binding of prolactin, PRLR commences a signal transduction pathway which

ultimately affects the transcription of genes associated with reproductive success and litter size, including the genes that encode the milk proteins necessary for lactogenesis, such as β-casein and α-lactalbumin. (Specification, p. 3). One seeking to find a gene that may have an effect on litter size would thus have a multitude of potential genes to choose from, even in the prolactin pathway (specification, p. 2-4). Applicant's invention relates to the discovery that the PRLR gene is a quantitative trait loci that has a measurable effect on litter size. (specification, p. 4). The size of a litter that a particular animal has is a complex trait influenced by a myriad of enzymes, receptors and metabolic pathways. The discovery that one gene in the pathway contributes a measurable effect on this phenotype is the crux of Applicant's invention. (specification 2-4). Once an association between a gene and a phenotypic trait has been identified it takes routine screening to find variability within that gene which will be useful as a marker for a particular phenotypic result. (specification, p. 5).

Genetic variability in the PRLR gene (and more specifically, in a region of this gene) in the form of polymorphisms have also been identified that allow an animal to be typed as an animal carrying genetic determinants for variation in litter size. (specification, p. 4). These variations can then be used to select females which are likely to produce larger litters (specification, p. 4) or males which might be included in a breeding program designed to develop breeding lines which produce larger litters (specification, p. 4).

Methods used to analyze and compare genomic sequences are well known to those skilled in the art. (specification, p. 5). In a preferred embodiment, the prolactin receptor gene of an animal is isolated and amplified using primers and DNA polymerase.

The amplified gene is then digested using restriction enzymes and the fragments are separated. This results in restriction fragment lengths which can be visualized using routine methods to those skilled in the art. (specification, p.6).

The present invention also relates to a method for identifying genetic variation in animals associated with a litter size in the PRLR gene or a specific region thereof. (specification, p. 4). Animals are bred and the number of offspring produced is determined. In a preferred method, restriction fragment length analysis is used to identify polymorphisms present in females producing larger litters. (specification, p. 6).

VII. ISSUES

The issues on appeal are:

A. Whether claims 1-3, 8-11, 16, 17, 19, 20, 26-29, 36-38, 54, and 55 were described in the specification in such a way as to reasonably convey to one skilled in the art of genetically typing animals that Applicant had possession of the claimed invention-the use of a specific region of the PRLR gene to identify genetic variation correlated with litter size in animals- at the time the application was filed.

B. Whether claims 1-3, 8-11, 16, 17, 19, 20, 26-29, 36-38, 54, and 55 are enabling to a person skilled in the art of genetically typing animals such that said person could use the invention commensurate in scope with claims which recite a specific region of the PRLR gene.

VIII. GROUPING OF THE CLAIMS

The claims do not stand or fall together. The patentability of the claims will be argued separately.

Claim 1 sets forth a method for screening animals to determine those more likely to produce larger litters comprising obtaining a sample of genetic material from said animal;

assaying for the presence of a genotype in the prolactin receptor gene sequence as set forth in SEQ ID NO: 3 or a region thereof in said sample, wherein said genotype is comprised of a polymorphism in the prolactin receptor gene associated with increased litter size; and

characterizing said animal.

Claim 2 further defines claim 1 by requiring that the method of assaying is selected from the group consisting of: restriction fragment length polymorphism (RFLP) analysis, heteroduplex analysis, single strand conformational polymorphism (SSCP), denaturing gradient gel electrophoresis (DGGE) and temperature gradient gel electrophoresis (TGGE).

Claim 3 further defines claim 1 by providing that the method of assaying for the presence of said polymorphism comprises the steps of digesting said genetic material with said restriction enzyme that cleaves the prolactin receptor gene in at least one place; separating the fragments obtained from said digestion; detecting a restriction pattern generated by said fragments; and comparing said pattern with a second restriction pattern for the pig prolactin receptor gene obtained by using said restriction enzyme, wherein said second restriction pattern is associated with increased litter size.

Claim 8 further defines claim 1 by requiring that the animal to be screened is a pig.

Claim 9 further defines claim 3 by requiring that the separation step is by gel electrophoresis.

Claim 10 further defines claim 3 by providing that the step of comparing said restriction patterns comprises identifying specific fragments by size and comparing the sizes of said fragments.

Claim 11 further defines claim 3 by requiring that prior to said digestion step, said gene or a portion thereof is amplified with a forward primer and a reverse primer.

Claim 16 further defines claim 3 by providing that said restriction site is located in the 3′ coding region of the pig prolactin receptor gene.

Claims 17 and 19 further define claim 3 by providing that said restriction site is located in the region between exons 8 and 9 of the prolactin receptor gene.

Claim 20 further defines claim 11 by requiring that said forward and reverse sequence primer is capable of amplifying a region of said pig prolactin receptor gene which contains a polymorphic AluI, HinFI, or HypCH4IV site.

Claim 26 further defines claim 20 by providing that said primers are selected from the group consisting of SEQ ID NO: 8 and 9 and SEQ ID NO: 10 and 11.

Claim 27 sets forth a method for identifying a genetic marker for litter size in animals comprising the steps of breeding male and female animals of the same breed or breed cross or derived from similar genetic lineages; determining the number of offspring produced by each female animal; determining the polymorphism in the prolactin receptor gene as set forth in SEQ ID NO: 3 of each female animal; and associating the number of

offspring produced by each female animal with said polymorphism thereby identifying a polymorphism for pig litter size.

Claim 28 further defines claim 27 by providing the additional step of selecting animals for breeding which are predicted to have increased litter size by said marker.

Claim 29 further defines claim 27 by requiring that said analysis comprises digestion of PCR amplified DNA with the restriction enzyme selected from the group consisting of AluI, HinFI, and HypCH4IV.

Claim 36 differs from the remaining independent claims in that it relates to a method of screening pigs to determine those more likely to produce larger litters by selecting for pigs with favorable combinations of alleles and therefore requires that the method for screening be done on pigs.

Claim 37 further defines claim 36 by requiring that the determination of prolactin receptor alleles comprises determining the presence of at least one allele associated with at least one DNA marker linked either directly or indirectly to a region of the gene set forth in SEQ ID NO: 3.

Claim 38 further defines claim 36 by providing that the DNA marker is a microsatellite.

Claim 54 differs from the remaining independent claims in that it relates to a method for identifying a marker correlated with litter size comprising the steps of obtaining a sample of genetic material from an animal, said sample comprising a prolactin receptor gene as set forth in SEQ ID NO: 3; assaying said prolactin receptor gene presented in said sample for a polymorphism; correlating whether a statistically significant association exists between said polymorphism and litter size in an animal of a

particular breed, strain, population, or group whereby said animal can be characterized for said marker.

Claim 55 further defines claim 54 by requiring that the screened animal is a pig.

IX. ARGUMENT

A. The Examiner has Failed to Present a Preponderance of Evidence to Rebut the Presumption of Adequate Written Description for Claims 1-3, 8-11, 16, 17, 19, 20, 26-29, 36-38, 54, and 55, Which Are Not Limited to a Single, Exemplified Polymorphism.

1. The Law of Written Description

The predecessor court to the Federal Circuit has stated "[a] description as filed is presumed to be adequate, unless or until sufficient evidence or reasoning to the contrary has been presented by the Examiner to rebut the presumption." *In re Marzocchi*, 439 F.2d 220, 224 (CCPA 1971). Thus the Examiner must have a reasonable basis to challenge the adequacy of the written description. *Id.* The Examiner has the initial burden of presenting by a preponderance of the evidence why a person skilled in the art would not recognize in Applicants' disclosure a description of the invention defined by the claims. *In re Wertheim*, 541 F.2d 257, 262 (CCPA 1976). In rejecting claims, the Examiner must set forth express findings of fact regarding the above analysis which support the lack of written description conclusion. Id.

Applicants "are not required to disclose every species encompassed by their claims even in an unpredictable art". *Regents of University of California v. Eli Lilly*, 119 F.3d 1559, 1569 (Fed. Cir. 1997). This issue is further addressed in the USPTO's Written Description Guidelines:

A representative number of species means that the species which are adequately described are representative of the entire genus. Thus, when there is substantial variation within the genus, one must describe a sufficient variety of species to reflect the variation within the genus. On the other hand, there may be situations where one species adequately supports a genus. What constitutes a "representative number" is an inverse function of the skill and knowledge in the art. Satisfactory disclosure of a "representative number" depends on whether one of skill in the art would recognize that the applicant was in possession of the necessary common attributes or features of the elements possessed by the member of the genus in view of the species disclosed. For inventions in an unpredictable art, adequate written description of a genus which embraces widely variant species cannot be achieved by disclosing only one species within the genus. *Description of a representative number of species does not require the description to be of such specificity that it would provide individual support for each species that the genus embraces.*
(emphasis added)

It is thus not necessary that the specification describe each individual species embraced by a genus claim. Instead, whether an adequate description has been made of a genus claim is determined by whether or not a sufficient variety of species has been described to reflect variation within the genus and whether one skilled in the art would recognize that the Applicant was in possession of the "common attributes or features of the elements possessed by the member of the genus in view of the species disclosed." *See, e.g., Regents of University of California*, 119 F.3d at 1569 (stating that "[a] description of a genus of cDNAs may be achieved by means of a recitation of a representative number of cDNAs, defined by nucleotide sequence, falling within the scope of the genus or of a recitation of structural features common to the members of the genus, which features constitute a substantial portion of the genus").

The Federal Circuit has recently defined the means by which genetic material may be adequately described. The written description requirement may be met by "show[ing] that an invention is complete by disclosure of sufficiently detailed, relevant identifying characteristics . . . i.e., complete or partial structure, other physical and/or chemical

properties, *functional characteristics when coupled with a known or disclosed correlation between function and structure,* or some combination of such characteristics." *Enzo Biochem, Inc. v. Gen-Probe Inc.*, 63 USPQ2d 1609, 1613 (Fed. Cir. 2002).

2. The Examiner's Conclusion of Lack of Written Description is Based on an Inadequate Application of the Law to the Claimed Invention

Claims 1-3, 8-11, 16, 17, 19, 20, 26-29, 36-38, 54 and 55, which claim the PRLR gene or a region thereof rather then specific polymorphisms, stand rejected as containing subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention. Applicant's invention relates to the association of the region of the prolactin receptor gene as set forth in SEQ ID NO: 3 to the phenotypic trait of increased litter size. The genus of nucleic acids encompassed by Applicant's claims all share the common attribute of being quantitative trait loci that have a measurable effect on litter size that are all within SEQ ID NO: 3.

The Examiner states that the "claims encompass a genus of nucleic acids which comprise prolactin receptor polymorphisms which are not disclosed in the specification" and "no common element or attributes of the sequences are disclosed which would permit selection of sequences as polymorphisms." The Examiner further states that "[n]o structural limitations or requirements which provide guidance on the identification of sequences which meet these functional limitations of associating a polymorphism with litter size is provided." (7/23/2003 Office Action, p. 2-3).

The rejection is believed improper for the following reasons.

Amended claim 1 contains the structural features by requiring that the genotype assayed for is variation present in the prolactin receptor gene as set forth in, or a region therein, of SEQ ID NO: 3. Claim one also requires that the screened animal's prolactin receptor gene variant is associated with an increased litter size. The claim therefore also requires a particular function. Support for this is present in the specification by disclosure of three separate polymorphisms which are associated with increased litter size. Identification of the relevant polymorphism is the means by which one practices the invention, i.e., the association between the prolactin receptor gene and increased litter size. The claim thereby recites a structural feature which is common to all members of the genus (a specific region of a DNA sequence) and additionally requires a particular function (causes a phenotypic difference in litter size).

Amended claim 27 also contains the necessary structural features by requiring that the polymorphism used to genetically mark the animal be located in the prolactin receptor gene set forth in SEQ ID NO: 3. Moreover, claim 27 also requires that the number of offspring produced by said animal be associated with the polymorphism, thereby identifying a polymorphism for litter size. Claim 27 thus also requires a particular function and specifically excludes polymorphisms which do not carry the association, and also contemplates that one must correlate the particular allele to litter size for a given population before a certain polymorphisms can be used as a marker.

Amended claim 36 contains the necessary structural feature by requiring that the alleles which are to be determined in said animal are contained within the prolactin receptor gene of SEQ ID NO: 3. Additionally, the claim also requires a particular function in that the alleles to be determined are to be associated with litter size.

Finally, amended claim 54 also contains the necessary structural feature by requiring that the sample of genetic material obtained from the animal contains the prolactin receptor gene as set forth in SEQ ID NO: 3. The claim also contains a functional requirement in that the polymorphism identified in the prolactin receptor must be correlated with litter size.

The present claims all require that the genetic material which is to be assayed is the prolactin receptor gene as set forth in SEQ ID NO: 3. The invention thus describes a particular and definite structure and does not read on "widely variant species". The polymorphisms which are used to associate an animal's prolactin receptor gene with an increased litter size are all contained within the disclosed SEQ ID NO: 3. The Application discloses how one can identify a particular polymorphism within the prolactin gene set forth in SEQ ID NO: 3:

> As used herein, the designation of a particular polymorphism is made by the name of a particular restriction enzyme. This is not intended to imply that the only way the site can be identified is by the use of that restriction enzyme. There are numerous databases and resources available to those of skill in the art to identify other restriction enzymes which can be used to identify a particular polymorphism, for example http://darwin.bio.geneseo.edu which can give restriction enzymes upon analysis of a sequence and the polymorphism to be identified. In fact as disclosed in the teachings herein there are numerous ways of identifying a particular polymorphism or allele with alternate methods which may not even include a restriction enzyme, but which assay for the same genetic or proteomic alternative form.
> (specification, p. 7).

There is thus great detail in the specification as to how other polymorphisms in this gene may be identified.

The Applicants have disclosed at least three polymorphisms that have been identified which correlate with a phenotypic difference in litter size. These polymorphisms are identified in the Application using the restriction enzymes AluI,

HinFI, and Hpych21V. See specification, Examples 6 and 7, pages 35-51. While every polymorphism present in the PRLR gene may not be associated with an increase in litter size, this does not negate written description as there is ample description of how to locate polymorphisms and how to correlate them to phenotypic traits. As the data set forth in Example 7 shows (specification, p. 38-54), various polymorphisms will have various associations with litter size and this may vary with different populations. Claim 27 specifically recites that one must first conduct an association analysis to identify which polymorphism may be associated with the trait of interest for a given population. The fact that there may exist other polymorphisms which are not useful as predictors of phenotypic traits does not negate patentability under 112. Applicant clearly had possession of and discloses the structure of the ultimate target, which is Applicant's invention i.e. that prolactin is a major effect gene for litter size. Even within the gene, Applicant has described a particular region to use as a target. Applicants have thus shown that they were in possession of a method of identifying animals with increased litter size by assaying for the presence of a genotype in the prolactin receptor gene as set forth in SEQ ID NO:3 and correlating this with phenotypic variability.

3. Conclusion as to Written Description

For the above-stated reasons, the Applicant has demonstrated that the Examiner has failed to show, by a preponderance of the evidence, that the invention was described such that a person skilled in the art would recognize that the Applicant was in possession of the invention at the time the Application was filed. Appellant therefore respectfully requests that the Examiner's rejection under 35 U.S.C. § 112, first paragraph be reversed.

B. The Examiner has Failed To Rebut the Presumption of Enablement for Claims 1-3, 8-11, 16, 17, 19, 20, 26-29, 36-38, 54, and 55.

1. The Law Of Enablement

The Federal Circuit has stated:

> [A] specification disclosure which contains a teaching of the manner and process of making and using the invention in terms which correspond in scope to those used in describing and defining the subject matter sought to be patented must be taken as in compliance with the enabling requirement of the first paragraph of section 112 unless there is reason to doubt the objective truth of the statements contained therein which must be relied on for enabling support.

In re Brana, 51 F.3d 1560, 1566 (Fed. Cir. 1995), *citing, In re Marzocchi*, 439 F.2d 220, 223 (C.C.P.A. 1971). There is thus a presumption that the Applicant's disclosure is valid. *Id.*

The test for enablement under § 112, first paragraph, is "whether or not the specification contains a sufficiently explicit disclosure to enable one having ordinary skill in the relevant field to practice the invention claimed therein without the exercise of undue experimentation." *Ex Parte Forman*, 230 U.S.P.Q. 546 (Bd. Pat. App. & Int'f 1986). Several factors may be considered in determining whether a specification is enabling. Although none of these factors are controlling and not all of them need be considered, they are illustrative: (1) the quantity of experimentation necessary, (2) the amount of direction or guidance presented, (3) the presence or absence of working examples, (4) the nature of the invention, (5) the state of the prior art, (6) the relative skill of those in the art, (7) the predictability or unpredictability of the art, and (8) the breadth of the claims. *In re Wands*, 8 USPQ2d 1400, 1404 (Fed. Cir. 1988). Experimentation is permissible if it is routine and if guidance is provided directing such experimentation such that one skilled in the art would be able to practice an embodiment of the invention. *Ex Parte Forman*, 230 U.S.P.Q. at 547.

2. The Examiner's Conclusion of Lack of Non-Enablement is Based on an Inadequate Application of the Law to the Claimed Invention

Claims 1-3, 8-11, 16, 17, 19, 20, 26-29, 36-38, 54 and 55 stand rejected as being non-enabling such that a person skilled in the art could use the invention commensurate in scope with the claims. The examiner states that while the specification is "enabling for some polymorphisms in the porcine prolactin receptor such as the Alu polymorphism, [it] does not reasonably provide enablement for all polymorphisms . . . ." The Examiner then applies the factors recited in *In re Wands* in concluding that the specification is non-enabling. Specifically, the Examiner states "there is no assurance or even likelihood of success, since there is no reason to believe that other polymorphisms necessarily exist which have the desired correlation." (7/23/2003 Office Action, p. 7-12).

This rejection is believed improper for the following reasons.

Applicant's invention relates to variation in the prolactin receptor gene as set forth in SEQ ID No: 3 is associated with phenotype. The identification of additional polymorphisms is routine and there is ample description in the specification for identification of other polymorphisms. A claim as narrow as the Examiner suggests would allow a potential infringor to use the same quantitative trait loci identified by Applicant but assay for it with different polymorphisms and thus avoid infringement.

The molecule prolactin is an anterior pituitary peptide hormone involved in many aspects of an animal's reproductive success. Prolactin activity is mediated by its receptor (PRLR), a member of the cytokine/GHR/PRLR superfamily. Upon the binding of prolactin, PRLR commences a signal transduction pathway likely involving the tyroskine kinase Jak2. The signal transduction pathway mediated by PRLR has multiple targets,

including the genes that encode the milk proteins necessary for lactogenesis, such as β-casein and α-lactalbumin. (specification, p. 3).

The Applicant's invention relates to the discovery that genetic variation in the prolactin receptor gene can have a phenotypic effect on the litter size of a particular animal. Polymorphisms exist within the prolactin receptor gene which allow one skilled in the art to select those animals which are likely to produce larger litters. Identification of a particular polymorphism within an animal is routine to one skilled in the art. The initial step involves isolation of an animal's DNA:

> In the present invention, a sample of genetic material is obtained from a pig. Samples can be obtained from blood, tissue, semen, etc. Generally peripheral blood cells are used as the source, and the genetic material is DNA. A sufficient amount of cells are obtained to provide a sufficient amount of DNA for analysis. This amount will be known or readily determinable by those skilled in the art. The DNA is isolated from the blood cells by techniques known to those skilled in the art. (specification, p. 10).

The DNA is then assayed for the presence of a polymorphism using techniques well known in the art:

> Any method of identifying the presence or absence of this marker may be used, including for example single-strand conformation polymorphism (SSCP) analysis, base excision sequence scanning (BESS), RFLP analysis, heteroduplex analysis, denaturing gradient gel electrophoresis, and temperature gradient electrophoresis, allelic PCR, ligase chain reaction direct sequencing, mini sequencing, nucleic acid hybridization, micro-array-type detection of the prolactin gene, or other linked sequences of the prolactin receptor gene and examination for the markers in the 3' translated and nontranslated region (specification, p. 10).

A specific example of isolating and identifying a polymorphism within the prolactin receptor is provided in Example 2, pages 28-29.

Moreover, because the Applicants have identified at least three polymorphisms within the prolactin receptor gene, the isolation of additional polymorphisms is now both expected and routine:

> The methods and materials of the invention may also be used more generally to evaluate pig DNA, genetically type individual pigs, and detect genetic differences in pigs. In particular, a sample of pig genomic DNA may be evaluated by reference to one or more controls to determine if a polymorphism in the prolactin receptor gene is present. Preferably, RFLP analysis is performed with respect to the pig prolactin receptor gene, and the results are compared with a control. The control is the result of a RFLP analysis of the pig prolactin receptor gene of a different pig where the polymorphism of the prig prolactin receptor gene is known. Similarly, the prolactin receptor genotype of a pig may be determined by obtaining a sample of its genomic DNA, conducting RFLP analysis of the prolactin receptor gene in the DNA, and comparing the results with a control. Again, the control is the result of RFLP analysis of the prolactin receptor gene of a different pig. The results genetically type the pig by specifying the polymorphism in its prolactin receptor genes. Finally, genetic differences among pigs can be detected by obtaining samples of the genomic DNA from at least two pigs, identifying the presence or absence of a polymorphism in the prolactin receptor gene, and comparing the results. (specification, p. 25).

Once a polymorphism within the prolactin receptor gene has been identified, one skilled in the art would be able to perform routine experimentation in order to associate that polymorphism with litter size. "Those skilled in the art can generate snps from this region, conduct association studies as illustrated here, so as to determine which marker or combination of markers can be used to select for those animals likely to have a higher breeding value for litter size." (specification, p. 51). An example of an association study is provided in the specification. See Example 7, pages 38-51.

3. Conclusion as to Enablement

For the above-stated reasons, there is insufficient evidence of record for the Examiner to have rebutted the presumption of lack of enablement. Appellant therefore respectfully requests that the Examiner's rejection under 35 U.S.C. § 112, first paragraph be reversed.

X. CONCLUSION

For the above-stated reasons, it is submitted that the claims are in a condition for allowability. The decision of the Examiner, therefore, should be reversed and the case allowed.

Enclosed herein please find the Appeal Brief in triplicate. Please also consider this a request for a two-month extension of time, therefore, enclosed is our check for $750.00 to cover the cost of the two-month extension ($420.00) and the Appeal Brief ($330.00). Any deficiency or overpayment should be charged or credited to Deposit Account 26-0084.

Respectfully submitted,

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APPENDIX

Claim 1 (Previously presented): A method for screening animals to determine those more likely to produce larger litters comprising:

obtaining a sample of genetic material from said animal;

assaying for the presence of a genotype in the prolactin receptor gene sequence as set forth in SEQ ID NO: 3 or a region thereof in said sample, wherein said genotype is comprised of a polymorphism in the prolactin receptor gene associated with increased litter size; and

characterizing said animal.

Claim 2 (Original): The method of claim 1 wherein said step of assaying is selected from the group consisting of: restriction fragment length polymorphism (RFLP) analysis, heteroduplex analysis, single strand conformational polymorphism (SSCP), denaturing gradient gel electrophoresis (DGGE) and temperature gradient gel electrophoresis (TGGE).

Claim 3 (Previously Presented): The method of claim 1 wherein said step of assaying for the presence of said polymorphism comprises the steps of:

digesting said genetic material with said restriction enzyme that cleaves the prolactin receptor gene in at least one place;

separating the fragments obtained from said digestion;

detecting a restriction pattern generated by said fragments; and

comparing said pattern with a second restriction pattern for the pig prolactin receptor gene obtained by using said restriction enzyme, wherein said second restriction pattern is associated with increased litter size.

Claim 4 (Withdrawn): The method of claim 3 wherein said restriction enzyme is AluI.

Claim 5 (Withdrawn): The method of claim 3 wherein said restriction enzyme is HinFI.

Claim 6 (Withdrawn): The method of claim 3 wherein said restriction enzyme is HypCH4IV.

Claim 7 (Cancelled)

Claim 8 (Original): The method of claim 1 wherein said animal is a pig.

Claim 9 (Original): The method of claim 3 wherein said separation is by gel electrophoresis.

Claim 10 (Original): The method of claim 3 wherein said step of comparing said restriction patterns comprises identifying specific fragments by size and comparing the sizes of said fragments.

Claim 11 (Previously Presented): The method of claim 3 further comprising, prior to said digestion step, amplifying said gene or a portion thereof with a forward primer and a reverse primer.

Claim 12 (Withdrawn): The method of claim 3 wherein said polymorphism is a polymorphic AluI restriction site.

Claim 13 (Withdrawn): The method of claim 3 wherein said polymorphism is a polymorphic HinFI restriction site.

Claim 14 (Cancelled)

Claim 15 (Withdrawn): The method of claim 3 wherein said polymorphism is a polymorphic HypCH4IV restriction site.

Claims 16 (Previously presented): The method of claim 3 wherein said restriction site is located in the 3′ coding region of the pig prolactin receptor gene.

Claim 17 (Previously presented): The method of claim 3 wherein said restriction site is located in the region between exons 8 and 9 of the prolactin receptor gene.

Claim 18 (Cancelled)

Claims 19 (Previously presented): The method of claim 3 wherein said restriction site is located in the region between exons 8 and 9 of the prolactin receptor gene.

Claim 20 (Previously presented): The method of claim 11 wherein said forward and reverse sequence primer is capable of amplifying a region of said pig prolactin receptor gene which contains a polymorphic AluI, HinFI, or HypCH4IV site.

Claim 21 (Withdrawn): The method of claim 20 wherein said forward and reverse primers are selected from and based upon SEQ ID NO: 3.

Claim 22 (Withdrawn): The method of claim 20 wherein said primers are SEQ ID NO: 4 and SEQ ID NO: 5.

Claim 23 (Withdrawn): The method of claim 20 wherein said primers are SEQ ID NO: 6 and SEQ ID NO: 7.

Claim 24 (Withdrawn): The method of claim 22 wherein said forward primer is selected from the group consisting of SEQ ID NO: 1 and SEQ ID NO: 6 and said reverse primer is selected from the group consisting of SEQ ID NO: 2 and SEQ ID NO: 7.

Claim 25 (Withdrawn): The method of claim 22 wherein said primer set comprise SEQ ID NO: 1 and SEQ ID NO: 2.

Claim 26 (Previously presented): The method of claim 20 wherein said primers are selected from the group consisting of SEQ ID NO: 8 and 9; and SEQ ID NO: 10 and 11.

Claim 27 (Previously presented): A method for identifying a genetic marker for litter size in animals comprising the steps of:

breeding male and female animals of the same breed or breed cross or derived from similar genetic lineages;

determining the number of offspring produced by each female animal;

determining the polymorphism in the prolactin receptor gene as set forth in SEQ ID NO: 3 of each female animal; and

associating the number of offspring produced by each female animal with said polymorphism thereby identifying a polymorphism for pig litter size.

Claim 28 (Original): The method of claim 27 further comprising the step of selecting animals for breeding which are predicted to have increased litter size by said marker.

Claim 29 (Previously presented): The method of claim 27 wherein said analysis comprises digestion of PCR amplified DNA with the restriction enzyme selected from the group consisting of AluI, HinFI, and HypCH4IV.

Claim 30-34 (Cancelled)

Claim 35 (Withdrawn): A DNA sequence from the pig prolactin receptor gene 3' translated and nontranslated region, said sequence consisting of SEQ ID NO: 3.

Claim 36 (Previously Presented): A method for screening pigs to determine those more likely to produce larger litters, and/or those less likely to produce larger litters, which method comprises of the steps:
determining the alleles of prolactin receptor present in a pig having SEQ ID NO: 3;
determining the alleles of other markers for genes known to affect litter size; and
selecting for animals with favorable combinations of alleles and against those carrying unfavorable combinations.

Claim 37 (Previously presented): The method of claim 36 wherein the determination of prolactin receptor alleles comprises determining the presence of at least one allele associated with at least one DNA marker linked either directly or indirectly to a region of the gene set forth in SEQ ID NO: 3.

Claim 38 (Original): The method as claimed in claim 36 wherein the DNA marker is a microsatellite.

Claim 39 (Withdrawn): The method as claimed in claim 36 wherein the DNA marker is SW1305, S0077, S0006, SW2411, SW1035 and S0111.

Claim 40-41 (Cancelled)

Claim 42 (Withdrawn): The method of claim 41 wherein said forward primer is SEQ ID NO: 1 and said reverse primer is SEQ ID NO: 2.

Claim 43 (Withdrawn): The method of claim 41 wherein said forward primer is SEQ ID NO: 8 and said reverse primer is SEQ ID NO: 9.

Claim 44 (Withdrawn): The method of claim 41 wherein said forward primer is SEQ ID NO: 10 and said reverse primer is SEQ ID NO: 11.

Claim 45 (Cancelled)

Claim 46 (Withdrawn): The method of claim 40 wherein said marker is AluI.

Claim 47 (Withdrawn): The method of claim 40 wherein said marker is HinFI.

Claim 48 (Withdrawn): The method of claim 40 wherein said marker is HypCH4IV.

Claim 49 (Cancelled)

Claim 50 (Withdrawn): The method of claim 40 wherein said restriction fragment pattern is characterized by a 124 bp fragment, a 110 bp fragment, a 79 bp fragment, a 77 bp fragment, and a 67 bp fragment.

Claim 51 (Withdrawn): The method of claim 40 wherein said restriction fragment pattern is characterized by a 103 bp fragment, an 86 bp fragment, and a 17 bp fragment.

Claim 52 (Withdrawn): The method of claim 40 wherein said restriction fragment pattern is characterized by the pattern as shown in Figure 7.

Claim 53 (Withdrawn): The method of claim 40 wherein said restriction fragment pattern is characterized by a 281 bp fragment and a 140 bp fragment.

Claim 54 (Previously presented): A method for identifying a marker correlated with litter size comprising the steps of:

obtaining a sample of genetic material from an animal, said sample comprising a prolactin receptor gene as set forth in SEQ ID NO: 3;

assaying said prolactin receptor gene presented in said sample for a polymorphism;

correlating whether a statistically significant association exists between said polymorphism; and

litter size in an animal of a particular breed, strain, population, or group whereby said animal can be characterized for said marker.

Claim 55 (Previously Presented): The method of claim 54 wherein said animal is a pig.